

Different adjuvant chemotherapy regimens in older breast cancer patients?

Adjuvant chemotherapy for early breast cancer patients improves survival in general, but estimating true benefit on the individual level remains a challenge, especially for older individuals. There are some data suggesting that older individuals, certainly those at higher risk of relapse, can indeed derive benefit from adjuvant chemotherapy, and this therapy should certainly not be denied on the basis of age alone, if only to ensure equal access to health care [1, 2]. There are many studies showing provocatively much lower use of adjuvant chemotherapy in older people probably because of fear for toxicity and futile treatment [1, 2], but also very likely, although poorly reported, because goals in life shift throughout the course of lifetime from mere quantity of life to more quality of life. Older patients more often die of other causes than breast cancer and treatment side-effects can seriously affect quality of life. However, let us not forget that elderly breast cancer patients also die more often of breast cancer [3], demonstrating that under-treatment, the other extreme position mirroring overtreatment, can negatively affect outcome.

If the decision to administer adjuvant chemotherapy is made for an individual old person, the next question is the choice of the regimen. Unfortunately, most frequently used regimens have been studied in younger fit populations. Some studies have included a proportion of patients above age 70, but actually rather a selection of fitter elderly, not representative of the general population, while previous studies [4] have even debarred those above age 70 from participation.

There are many reports showing higher toxicity with standard adjuvant chemotherapy regimens when age increases [1, 2]. Hospitalization rate is also clearly higher in the elderly [5]. In the adult population, the classical CMF regimen (cyclophosphamide, methotrexate, fluorouracil) has largely and progressively been replaced by anthracyclines-based regimens, and later by sequential or combined anthracycline- and taxane-based regimens, because of improved efficacy [1]. However, the use of anthracyclines remains a sensitive matter because of the risk of cardiac failure, whose incidence increases with age [6]. Moreover, we are unaware of any solid evidence-based validation of sequential regimens in elderly, even when avoiding the approved 'high dose' of docetaxel (100 mg/m²) or the triplet TAC (docetaxel, doxorubicin, cyclophosphamide) combination [7], both highly myelosuppressive, especially in elderly for whom baseline neutrophil counts are often misleading to estimate bone marrow functional

reserve. For all these reasons, there is a tendency to bypass these standard regimens developed in younger adults when treating elderly patients, referring to empirically adjusted ones especially in those patients who are not 100% fit and who represent the most important segment of the elderly population. Few attempts have been done to develop elderly specific strategies.

The ELDA trial published in this journal [8] is such an example. The study randomized 302 women aged 65–79 years, operated for breast cancer, with average to high risk of recurrence, to CMF or weekly docetaxel for 4–6 cycles according to hormone-receptor status. In contrast to the assumption, docetaxel did not improve outcome compared with CMF [HR for disease-free survival (DFS) 1.21; *P* = 0.32]. Haematological toxicity was less pronounced for docetaxel, but non-haematological toxicity and quality of life were conversely significantly worse: of note, two cases of intestinal necrosis events yielding 1.36% toxic death rate certainly do not match the definition of 'soft chemotherapy'. However, the authors are to be congratulated for performing and finishing a randomized trial in the older population. Several trials in the past (CASA trial, ACTION trial) have failed to do this, supposedly because of the difficulty to convince elderly for trial participation [9] which actually may be an emotional interpretation rather than a fair and objective one. Only one large adjuvant trial in this population has been published recently [10], showing that a 'soft' oral adjuvant chemotherapy regimen with capecitabine is clearly inferior to standard chemotherapy, CMF or AC (adriamycin, cyclophosphamide).

How should we interpret the results of the ELDA trial in this context?

First, it must be acknowledged that both arms (CMF or docetaxel weekly) are not standard adjuvant regimens. Weekly docetaxel has not been previously studied as 'monotherapy', and when used after anthracyclines, it is clearly more toxic than weekly paclitaxel in the general population [11]; CMF is generally considered inferior to regimens combining anthracyclines and taxanes, as mentioned before. Taken together with the observed toxicity in the ELDA trial, this does not encourage the use of either regimen in the older population despite the lack of direct comparisons with less fuddy-duddy regimens. Because of this poor situation, we end up selecting regimens studied in the general population that are potentially and safely usable in the elderly. Sequential regimens like AC followed by weekly paclitaxel are certainly feasible, but only in fit older patients, not forgetting that age remains a clear risk factor for anthracycline-related cardiotoxicity. Although attractive, weekly paclitaxel monotherapy in the general (not high-risk) population [12] did not achieve non-inferiority compared with AC (HR for relapse free survival 1.26), so cannot be recommended. The TC (docetaxel cyclophosphamide) regimen [13] is an attractive option for elderly since it was superior to AC for DFS and overall survival (OS) irrespective of

age, limiting the exposure to anthracyclines. It seems feasible in the older population [13, 14] on the proviso that prophylactic granulocyte-colony-stimulating growth factor is used. Liposomal anthracyclines also have the potential advantage of reduced cardiotoxicity and are feasible in elderly [15], but there are no data on efficacy in adjuvant setting.

A second issue is that ~20% of the ELDA population was HER2 positive, and only part of this group received adjuvant trastuzumab. However, no details are provided in the report and this subgroup is too small in any case to allow solid conclusions. Adjuvant chemotherapy regimen selection in HER2-positive disease is certainly different story. Like in HER2-negative cases, a classical sequential chemotherapy as AC followed by weekly paclitaxel, combined for this purpose with trastuzumab, could be a good treatment choice for certain patients. But the use of two independently cardiotoxic drugs may put patients at risk of additive, if not synergistic, cardiac risk, increasing *per se* according to age [16]. That the adjuvant trastuzumab pivotal trials included only a small amount of elderly patients unfortunately nurtures a significant or ambiguous grey zone on the safety of such combined treatments. The TCH (docetaxel, carboplatin trastuzumab) regimen might be of interest specifically for elderly since it does not contain anthracyclines and performs more or less similar to standard anthracycline and taxane regimens in terms of outcome, having much less cardiac toxicity [4]. However, the study which assessed its value had an upper age cut-off of 70 years, so there are no data on elderly at all. Furthermore, the high dose of carboplatin (AUC 6) in combination with docetaxel makes this schedule very unrealistic for the majority of older patients. Although not specifically investigated in elderly, there are recent single-agent phase II data using an anthracycline-free regimen that could be of interest for older patients with low- and intermediate-risk of relapse or who present with comorbidities that could increase cardiotoxicity. In an open-label phase II study, predominantly in node-negative patients, the non-anthracycline TC (docetaxel, cyclophosphamide) combination with trastuzumab was effective in preventing recurrence of breast cancer down to <3% after a median follow-up of 3 years [17]. More recently, data have been orally presented on the combination of weekly paclitaxel and trastuzumab in node-negative HER2-positive disease [18]. As in the former study, the relapse rate was encouragingly low (3-year DFS 98.7%) and the combination seemed well tolerated, although taking a closer look at neurotoxicity will be critical. Thus, these two regimens have emerged as acceptable options for individual cases where avoidance of anthracycline-related cardiotoxicity is important. They still disagree with the general message of inferiority of single versus combination regimens, and as such deserve further scientific validation.

Last but not least, a major strength of the ELDA trial is the inclusion of geriatric assessment (GA). This has hardly been integrated in clinical trials in the past. It provides crucial information about the general health status of included patients [19], and allows potentially refined analysis for identification of subgroups that will benefit more or less treatment. In the ELDA trial, both instrumental activities of daily living and comorbidities were independently associated with severe non-haematological toxicity. GA correlating with survival and treatment toxicity, it could therefore contribute to a more individualized

treatment choice in older individuals [20], as advocated by the International Society of Geriatric Oncology (SIOG) in its 10 priorities [21].

In conclusion, the ELDA trial is another building block to a better definition of adjuvant treatment in older breast cancer patients. Adapted and supposedly so-called soft chemotherapy regimens, such as capecitabine or weekly docetaxel as in ELDA trial, are not necessarily better than old-fashioned although standard ones. The ELDA study does not define 'the' new standard regimen for elderly. More importantly, it shows how eagerly awaited future research in this domain should be done, such as the ongoing ASTER 70s phase III trial (EudraCT 2011-004744-22) [22] running in France and Belgium, in order to improve equity and solidarity in health cares.

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disclosure

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